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Signed R. Mahoney

Dated 18 October 2002

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Request for grant of a patent

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1.	Your reference	**4-32249P1/NFI 8003**
2.	Patent application number *(The Patent Office will fill in this part)*	**0202381.0**
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**NOVARTIS AG** **LICHTSTRASSE 35** **4056 BASEL** **SWITZERLAND**
	Patent ADP number *(if you know it)*	7125487001
	If the applicant is a corporate body, give the country/state of its incorporation	**SWITZERLAND**
4.	Title of invention	**Organic Compounds**
5.	Name of your agent *(If you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**B.A. YORKE & CO.** **CHARTERED PATENT AGENTS** **COOMB HOUSE, 7 ST. JOHN'S ROAD** **ISLEWORTH** **MIDDLESEX TW7 6NH**
	Patents ADP number *(if you know it)*	**1800001**

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	**Yes**

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Continuation sheets of this form	
Description	19
Claim(s)	2
Abstract	1
Drawing(s)	

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Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

B. A. Yorke & Co.

B.A. Yorke & Co. **01 February 2002**

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
020 8560 5847

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Organic compounds

The present invention relates to organic compounds having pharmaceutical e.g. IgE-synthesis inhibiting, activity.

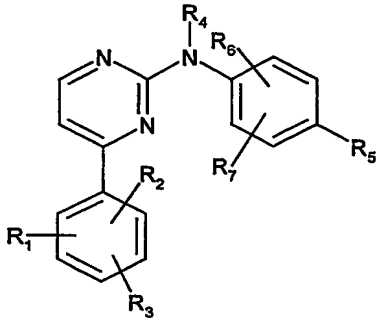
In one aspect the present invention provides the use of an amine, which is substituted by
- phenyl-substituted pyrimidin; and
- phenyl; and
- hydrogen or a third substituent,

in the preparation of a medicament for the treatment of IgE-synthesis-mediated diseases.

A third substitutent e.g. includes alkyl or a group of formula -CO-R_8, -CO-OR_9, -CO-CO-R_{10}, -CO-CO-OR_{11}, -CO-O-CO-R_{12}, -CO-N($R_{13}R_{14}$) or -SO_2-R_{15}, wherein R_8 and R_9 independently of each other are hydrogen, alkyl, cycloalkyl, aryl or heterocyclyl, R_{10}, R_{11} and R_{12} independently of each other are alky, cycloalkyl, aryl or heterocyclyl, R_{13} and R_{14} independently of each other are hydrogen ore alkyl, or one of R_{13} and R_{14} is hydrogen and the other is cycloalkyl, aryl or heterocyclyl, and R_{15} is hydroxy, alkyl or aryl, e.g. phenyl, p-toluene.

Preferably
- the pyrimidine is substituted by phenyl in position 4 of the pyrimidine ring;
- the pyrimidine is bound to the amine in position 2 of the pyrimidine ring;
- at least one of the phenyl rings bound to the amine or to the pyrimidine is substituted;
- at least one, preferably both, of the phenyl rings bound to the amine or to the pyrimidine, respectively, is/are substituted by halogen or haloalkyl.

In another aspect the present invention provides a compound of formula



I

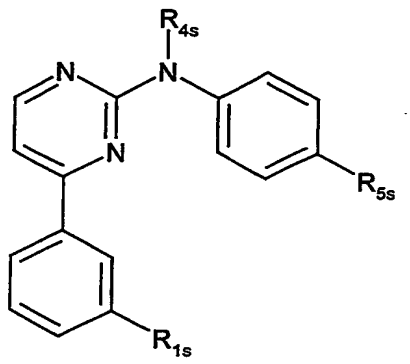
wherein

at least one of R_1, R_2 and R_3 is halogen or haloalkyl, and the other of R_1, R_2 and/or R_3 are independently of each other hydrogen, halogen or haloalkyl, R_5 is halogen or haloalkyl, R_6 and R_7 independently of each other are hydrogen, halogen, or haloalkyl, and
R_4 is hydrogen, alkyl, or a group of formula -CO-R_8, -CO-OR_9, -CO-CO-R_{10}, -CO-CO-OR_{11}, -CO-O-CO-R_{12}, -CO-N($R_{13}R_{14}$) or -SO_2-R_{15}, wherein
R_8, R_9 independently of each other are hydrogen, alkyl, cycloalkyl, aryl or heterocyclyl,
R_{10}, R_{11} and R_{12} independently of each other are alky, cycloalkyl, aryl or heterocyclyl,
R_{13} and R_{14} independently of each other are hydrogen ore alkyl, or one of R_{13} and R_{14} is hydrogen and the other is cycloalkyl, aryl or heterocyclyl, and
R_{15} is hydroxy, alkyl or aryl.

In a compound of formula I preferably
R_1 and R_2 are hydrogen and R_3 is halogen or haloalkyl,
R_4 and R_5 are as defined above,
R_6 is halogen or haloalkyl, and
R_7 is hydrogen.

In another aspect the present invention provides a compound of formula I, selected from the group consisting of
N-[4-(3-Chloro-phenyl)-pyrimidin-2-yl]-N-(4-chloro-3-trifluoromethyl-phenyl)-amine,
N-[4-(3-Trifluoromethyl-phenyl)-pyrimidin-2-yl]-N-(4-fluoro-3-trifluoromethyl-phenyl)-amine,
N-[4-(3-Trifluoromethyl-phenyl)-pyrimidin-2-yl]-N-(4-chloro-3-trifluoromethyl-phenyl)-amine,
N-[4-(3-Trifluoromethyl-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-amine, and
N-[4-(3-Chloro-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-amine,
wherein the amine group is unsubstituted or further substituted by R_4, wherein R_4 is as defined above.

In another aspect the present invention provides a compound of formula I which is a compound of formula



Is

wherein

R_{1s} is halogen or haloalkyl, preferably halogen, R_{5s} is halogen or haloalkyl, preferably haloalkyl and R_{4s} has the meaning of R_4 as defined above.

Preferably R_4 and R_{4s} are hydrogen, alkyl, e.g. (C_{1-6})alkyl, including unsubstituted alkyl or substituted alkyl, e.g. hydroxyalkyl; or a group of formula -CO-R_8, -CO-OR_9,-CO-CO-R_{10}, -CO-CO-OR_{11}, -CO-N($R_{13}R_{14}$) or -SO_2-R_{15}, wherein R_8, R_9, R_{10}, R_{11}, R_{13}, R_{14} and R_{15} are as defined above.

R_8 preferably is

- alkyl, more preferably (C_{1-8})alkyl, such as (C_{1-6})alkyl, e.g. methyl, ethyl, isobutyl, isopropyl, tert.butyl, e.g. including unsubstituted alkyl and substituted alkyl, e.g. alkoxyalkyl, such as (C_{1-4})alkoxyalkyl, alkylcarbonyloxy-alkyl, such as (C_{1-4})alkylcarbonyloxyalkyl,
- cycloalkyl, e.g. (C_{3-8})cycloalkyl, such as cyclopropyl, cyclohexyl,
- aryl, such as phenyl,
- heterocyclyl, e.g. heterocyclyl which is a 5 or 6-membered heterocyclic ring system, having 1 to 4, e.g. 1, heteroatoms, selected from N, O or S, e.g. O; such as tetrahydropyranyl.

R_9 preferably is alkyl, including unsubstituted alkyl and substituted alkyl, e.g.

- aminoalkyl, such as amino(C_{1-6})alkyl, alkylaminoalkyl, such as (C_{1-4})alkylamino(C_{1-4})alkyl, hydroxyalkylaminoalkyl, e.g. hydroxy(C_{1-4})alkylamino(C_{1-4})alkyl, e.g.dialkylaminoalkyl, e.g. di(C_{1-4})alkylamino(C_{1-4})alkyl, (hydroxyalkyl)(alkyl)aminoalkyl, such as [hydroxy(C_{1-4})alkyl] [(C_{1-4})alkyl]amino(C_{1-4})alkyl, (amino)(carboxy)alkyl, e.g. (amino)(carboxy)(C_{1-4})alkyl, alkylcarbonylaminoalkyl and alkylcarbonylaminoalkyl, e.g. (amino)(C_{1-4})alkylcarbonyl-amino(C_{1-6})alkyl, e.g. including ureidoalkyl, e.g. ureido(C_{1-4})alkyl, e.g. including alkylureidoalkyl and hydroxyalkylureidoalkyl, such as (hydroxy)(C_{1-4})alkylureido(C_{1-4})alkyl,
- carboxyalkyl, e.g. carboxy(C_{1-4})alkyl,
- hydroxyalkyl, e.g. hydroxy(C_{1-6})alkyl,
- alkoxyalkyl, e.g. (C_{1-4})alkoxy(C_{1-4})alkyl,

- alkylcarbonyloxyalkyl, e.g. including aminoalkylcarbonyloxyalkyl, such as (amino)(C_{1-4})alkylcarbonyloxy(C_{1-6})alkyl,
- heterocyclylalkyl, e.g. heterocyclyl(C_{1-4})alkyl, wherein heterocyclyl includes a 5- or 6-membered heterocyclic ring system having 1 to 4, e.g. 1 to 2, heteroatoms, selected from N, O or S, e.g. N, O, such as morpholinyl, pyrrolidinyl, piperazinyl, e.g. including unsubstituted heterocyclyl and substituted heterocyclyl, e.g. alkylheterocyclyl and hydroxyalkylheterocyclyl, such as (hydroxy)(C_{1-4})alkylheterocyclyl, e.g. heterocyclyl wherein the alkyl group is bound to the heterocyclic ring system via a heteroatom.

R_{10} preferably is aryl, e.g. phenyl,
R_{11} preferably is alkyl, e.g. (C_{1-4})alkyl.
R_{13} and R_{14} preferably are alkyl, e.g. (C_{1-4})alkyl.
R_{15} preferably is alkyl, e.g. (C_{1-4})alkyl.

In another aspect the present invention provides a compound of formula Is wherein R_{1s} is chloro, R_{5s} is trifluoromethyl and R_{4s} has the meaning of R_4 as defined above.

If not otherwise defined herein alkyl includes (C_{1-6})alkyl, e.g. (C_{1-4})alkyl. Aryl includes phenyl. Heterocyclyl includes a 5- or 6-membered heterocyclic ring system, having 1 to 4 heteroatoms selected from N, O, S, e.g. anellated with another ring system. Halogen includes fluoro, chloro, bromo. Haloalkyl includes halo(C_{1-4})alkyl, wherein halo is one or more halogen, preferably trifluoromethyl. Cycloalkyl includes (C_{3-8})cycloalkyl, e.g. (C_{3-6})cycloalkyl. Any group may be unsubstituted or substituted, e.g. substituted by groups as conventional in organic chemistry, e.g. including groups selected from halogen, haloalkyl, alkylcarbonyloxy, alkoxy, hydroxy, amino, alkylcarbonylamino, aminoalkylcarbonylamino, hydroxyalkylamino, aminoalkylamino, alkylamino, dialkylamino, heterocyclyl, alkylheterocyclyl, hydroxyalkylheterocyclyl, carboxyl, alkylcarbonyloxy, aminoalkylcarbonyloxy.

Compounds provided by the present invention are hereinafter designated as "compound(s) of the present invention". A compound of the present invention includes a compound in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate.

In another aspect the present invention provides a compound of the present invention in the form of a salt, or in the form of a salt and in the form of a solvate, or in the form of a solvate.

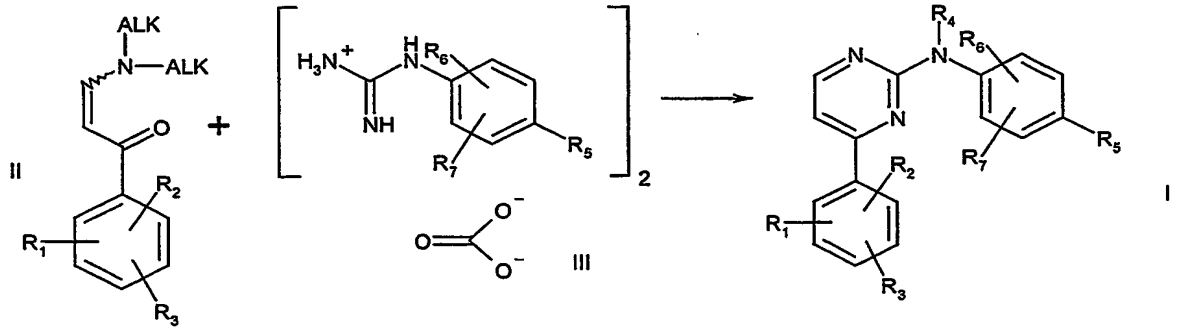
A salt of a compound of the present invention includes a pharmaceutically acceptable salt, e.g. including a metal salt or an acid addition salt. Metal salts include for example alkali or earth alkali salts; acid addition salts include salts of a compound of formula I with an acid, e.g. including inorganic and organic acids, e.g. including pharmaceutically acceptable acids, such as hydrochloric acid, sulfuric acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, tartaric acid.

A compound of the present invention in free form may be converted into a corresponding compound in the form of a salt; and vice versa. A compound of the present invention in free form or in the form of a salt and in the form of a solvate may be converted into a corresponding compound in free form or in the form of a salt in unsolvated form; and vice versa.

A compound of the present invention may exist in the form of isomers and mixtures thereof; e.g. optical isomers, diastereoisomers, cis trans conformers. A compound of the present invention may e.g. contain asymmetric carbon atoms and may thus exist in the form of enantiomeres, diastereoisomeres and mixtures thereof, e.g. racemates. E.g. a substitutent attached to an asymmetric carbon atom in a compound of the present invention may be in the R- or in the S-configuration, including mixtures thereof. A substituent Subst, e.g. alkyl, in a group -O-Subst as a part of a compound of the resent invention may be in the syn or in the anti form. The present invention includes a compound of the present invention in any isomeric form and in any isomeric mixture.

A compound of the present invention wherein the amine group is substituted by phenyl-substituted pyrimidin; and phenyl; and hydrogen may be prepared e.g. according, e.g. analogously, to a method as conventional, preferably according to the following reaction scheme 1:

SCHEME 1



e.g. wherein in a compound of formula I, II and III R_1, R_2, R_6, R_7, and R_8 are as defined above, and R_4 is H; and optionally further reacting a compound obtained with an appropriate reagent to obtain a compound of of the present invention wherein the amine group is

substituted by phenyl-substituted pyrimidin; and phenyl; and a third substitutent, e.g. a compound of formula I; wherein R_4 is as defined above, but other than hydrogen; e.g. reacting a compound of formula I wherein R_4 is H and the other substituents are as defined above with

- an alkyliodide in the presence of NaH, to obtain a compound of formula I wherein R_4 is alkyl,
- a bromo-hydroxyalkane to obtain a compound of formula I wherein R_4 is hydroxyalkyl,
- with a halogenide or an anhydride of a carboxylic acid of formula R_8COOH wherein R_8 is as defined above, to obtain a compound of formula I wherein R_4 is a group -CO-R_8, wherein R_8 is as defined above,
- with phosgene to obtain a compound of formula I wherein R_4 is -COCl and further reacting a compound obtained with a compound of formula R_9-OH, wherein R_9 is as defined above to obtain a compound of formula I wherein R_4 is a group of formula -CO-OR_9, wherein R_9 is as defined above,
- with a compound of formula R_{10}-CO-CO-Cl, wherein R_{10} is as defined above, to obtain a compound of formula I wherein R_4 is a group of formula -CO-CO-R_{10}, wherein R_{10} is as defined above,
- with a compound of formula R_{11}-O-CO-CO-Cl, wherein R_{11} is as defined above, to obtain a compound of formula I wherein R_4 is a group of formula -CO-CO-OR_{11}, wherein R_{11} is as defined above,
- with a compound of formula R_{12}-CO-O-CO-Cl, wherein R_{12} is as defined above, to obtain a compound of formula I wherein R_4 is a group of formula -CO-O-CO-R_{12}, wherein R_{12} is as defined above,
- with a compound of formula $(R_{13}R_{14})$N-CO-Cl, wherein R_{13} and R_{14} are as defined above, to obtain a compound of formula I wherein R_4 is a group of formula -CO-N($R_{13}R_{14}$), wherein R_{13} and R_{14} are as defined above,
- with a compound of formula R_{15}-SO_2-Cl, wherein R_{15} is as defined above, to obtain a compound of formula I wherein R_4 is a group of formula -SO_2-R_{15}, wherein R_{15} is as defined above.

Reactions of a compound of formula I wherein R_4 is H and the other substituents are as defined above with appropriate reagents to obtain a compound of formula I; wherein R_4 is as defined above, but other than hydrogen, are alkylation or acylation reactions and may be carried out as appropriate, e.g. according, such as analogously, to a method as conventional, e.g. or as described above. In such reactions substiutents, e.g. hydroxy or amine groups, may be protected before reaction and deprotected during or after reaction.

In another aspect the present invention provides a process for the production of a compound of formula I comprising reacting a compound of formula II wherein R_1, R_2 and R_3 are as defined above and ALK denotes alkyl or cycloalkyl, with a compound of formula III, wherein R_5, R_6 and R_7 are as defined above, to obtain a compound of formula I wherein R_1, R_2, R_3, R_5, R_6 and R_7 are as defined above, and R_4 is hydrogen, and optionally alkylating or acylating a compound obtained, e.g. and deprotecting groups if desired, to obtain a compound of formula I wherein R_1, R_2, R_3, R_5, R_6 and R_7 are as defined above, and R_4 is as defined above, but other than hydrogen, and isolating a compound of formula I obtained from the reaction mixture.

Any compound described herein, e.g. a compound of the present invention, may be prepared as appropriate, e.g. according to a method as conventional, e.g. or as described herein. Compounds of formula II and of formula III are known or may be obtained e.g. according to a method as conventional or as described herein.

The compounds of the present invention, e.g. including a compound of formula I, in free form or in the form of a salt, optionally in the form of a solvate, are hereinafter designated as "active compound(s) of the present invention".

The active compounds of the present invention exhibit pharmacological activity and are therefore useful as pharmaceuticals:

Immunoglobulin E (IgE) is critically involved in the pathogenesis and maintenance of allergic diseases such as atopic dermatitis, allergic asthma, allergic conjunctivitis and allergic rhinitis. To date, patients suffering from atopic dermatitis may be mainly treated with local or systemic glucocorticoids, ultraviolet light or, in severe cases, with immunosuppressants such as cyclosporin. Allergic asthma patients may be mainly treated with glucocorticoids or theophylline. Such compounds may suffer from various side effects and may not achieve the goal of reversal of disease progression in addition to alleviation of symptoms. It has been demonstrated recently that interference with IgE production or inactivation of its effector function once it has been synthesized in the body, may reduce allergic immune response and, consequently, may lead to amelioration of the disease. However, no specific inhibitor of IgE production in human B-lymphocytes is commercially available yet.

It has now been found that, the active compounds of the present invention may act as specific inhibitors of IgE synthesis. Upon systemic or oral administration an active compound of the present invention may suppress immunoglobulin synthesis, in particular the synthesis of immunoglobulin E in B-lymphocytes, i.e. an active compound of the present

invention may exhibit isotype specificity. Further it was found that an active compound of the present invention may not inhibit B-cell proliferation in concentrations below the concentrations needed to block IgE synthesis.

These activities can be shown in the following assays. The following abbreviations are used:

ELISA = enzyme-linked immunosorbent assay
FACS = fluorescence-activated cell sorting
IgE = immunoglobulin E
IL-4 = interleukin-4
IL-10 = interleukin-10
IMDM = Iscove's modified Dulbecco medium
SRBC = sheep red blood cells

1. <u>Isotype specificity</u>: Inhibition of immunoglobulin synthesis induced in primary human B-lymphocytes stimulated by cytokines and anti-CD40 antibody

Mononuclear cells are purified from normal human spleens. The resulting cell suspension contains 50-70% B-lymphocytes as judged by CD19 expression in a FACS analysis. Using 96-well round-bottomed microtiter plates (Costar) $5x10^4$ spleenocytes are set up in a final volume of 200 µl/well in IMDM. After pre-incubation with test compound for one hour the cells are cultured to induce IgE production for 9 days at 37°C in air supplied with 5 % CO_2 in the presence of 50 ng/ml of IL-4 and 500 ng/ml of anti-CD40 antibody. The culture cell supernatants are collected and quantitated for IgE by standard isotype specific sandwich ELISA. For the induction of IgG synthesis, the cells are cultured with 100ng/ml IL-10 and 500ng/ml of anti-CD40 antibody for the same time period before IgG levels are quantitated in the cell supernatants by isotype specific ELISA.
In these tests the active compounds of the present invention inhibit IgE production preferentially over IgG (IgG1).

2. <u>B-cell proliferation</u>

Normal human B-lymphocytes are purified from tonsils by removing contaminating T-cells with SRBC-rosetting according to M.S. Weiner et al. , Blood 42 (1973) 939. The resulting B-cells are more than 95% pure as judged by CD19 expression in a FACS analysis. Using 96-well round-bottomed microtiter plates (Costar) $1x10^5$ spleenocytes are set up in a final volume of 200 µl/well in IMDM. After pre-incubation with test compound for one hour, cell

proliferation is induced with 50ng/ml IL-4 and 500ng/ml anti-CD40 antibody. After a 4 day incubation period at 37°C in air supplied with 5 % CO_2, 1µCi of tritiated thymidine is added and the cells are cultured for ca. 16 hours. The cells are collected on a nitrocellulose filter and the DNA-bound radioactivity is quantitated by liquid scintillation counting.

In these tests active compounds of the present invention inhibit IL-4 and anti-CD40 antibody mediated B-cell proliferation above the concentrations needed to block IgE synthesis.

3. <u>Determination of stability of compounds of the present invention in plasma</u>

Heparinized blood is obtained from human volunteers and from Balb/c mice. Blood obtained is centrifuged for 4 minutes at 13,000 rpm at room temperature (RT) to obtain plasma. To aliquots of plasma (1 ml) test compounds, i.e. compounds of the present invention, are added (1 µl of 10 mM stock solutions in DMSO or water). The samples are incubated at 37°C. At various time points, aliquots of 100 µl are taken from said samples. An internal standard (5 µl of a 100 µg/ml solution of an internal standard compound in methanol) is added, followed by 300 µl of methanol (or acetonitrile or acetonitrile/1 M HCl, as required). Samples are centrifuged for 5 minutes at 13,000 rpm.

For analysis, 50 µl of the supernatants obtained are injected into an HPLC system (HP1090), equipped with a Hypersil BDS C-8 column (5 µm, 250x4.6 mm) plus pre-column (10x4.6 mm). The column is eluted isocratically at 55°C and at a flow rate of 1.5 ml/min with mixtures of acetonitrile and 10 mM $(NH_4)_2SO_4$, pH 2.7; the acetonitrile content of the mixtures used is in the range of 55 - 65 % for various substances.

Analysis of specific compounds, e.g. of a compound of example 8, may require a different HPLC-system, e.g. column: Zorbax Extend C18 (3.5 µm, 150x4.6 mm); pre-column: Hypersil BDS, C-8 (5 µm, 10x4.6 mm); RT; acetonitrile contents of solvent: 65 %.

UV detection is carried out at 277 nm. For calibration, plasma samples are spiked with a compound of example 1, or with a compound of formula II_{EX} wherein R_4 is as defined above, but other than hydrogen; both in the range of 0.5 to 20 µM, and internal standard. Absolute concentrations are calculated using these calibration sets.

In these determination tests it was found that a compound of formula II_{EX} wherein R_4 is as defined above, but other than hydrogen has a higher stability in plasma than a compound of example 1. From that it may be assumed that compounds of formula II_{EX} wherein R_4 is as defined above, but other than hydrogen, may be regarded as prodrugs of compounds of formula I, wherein R_4 is hydrogen. Compounds of formula I, wherein R_4 is hydrogen, on the other hand, may establish a highly active principle, e.g. may establish the basic structure for the surprising activity of a compound of the present invention which was found e.g. in ex

vivo tests. Compounds of formula I, wherein R_4 is hydrogen may thus be regarded as those compounds having the regular drug structure.

The active compounds of the present invention are therefore indicated for use as inhibitors of immunoglobulin synthesis, especially inhibitors of IgE synthesis, and are useful in the treatment of IgE-mediated diseases, particularly IgE-mediated allergic diseases, e.g. of diseases mediated by IgE expression, such as atopic dermatitis, particularly in children, urticaria, particularly acute urticaria, allergic asthma, allergic rhinitis, food allergies, allergic conjunctivitis, hayfever, bullous pemphigoid, industrial sensitization and chronic rejection of transplants.

For the above uses the dosage to be used will vary, of course, depending e.g. on the particular compound employed, the mode of administration and the treatment desired. However, in general satisfactory results may be obtained when the compounds are administered at a daily dosage of from about 1 mg/kg to about 30 mg/kg animal body weight, suitably given in divided doses two to four times daily. For most larger mammals the total daily dosage is from about 70 mg to about 2000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Unit dosage forms comprise, for example, from about 17.5 mg to about 1000 mg of compound in admixture with at least one solid or liquid pharmaceutically acceptable carrier or diluent.

An active compound of the present invention may be administered in similar manner to known standards such as glucocorticoids and antihistaminics for use in such indications. It may be admixed with conventional chemotherapeutically acceptable carriers and diluents and, optionally, further excipients, and administered e.g. orally in such forms, e.g. in the form of tablets, capsules; or, alternatively, it may be administered topically, e.g. in conventional forms, such as aerosols, ointments or creams; parenterally or intravenously. The concentration of active substance will, of course vary, e.g. depending on the compound administered, the treatment desired and the nature of the form. In general, however, satisfactory results may be obtained in topical application forms at concentrations of from about 0.05 % to about 5 %, particularly from about 0.1 % to about 1 % by weight.

In another aspect the present invention provides the use of an active compound of the present invention in the preparation of a medicament for the therapy of IgE-mediated diseases, e.g. of diseases mediated by IgE expression.

Pharmaceutical compositions for use in the therapy of IgE-mediated diseases may be prepared by mixing an active compound of the present invention together with at least one pharmaceutically acceptable carrier or diluent.

In another aspect the present invention provides a method of treatment of IgE-mediated diseases which comprises administering a therapeutically effective amount of an active compound of the present invention, e.g. in the form of a pharmaceutical composition, to a subject in need of such treatment.

An active compound of the present invention may be well tolerated, as may be determined according to a method as convential. An active compound of the present invention may possess beneficial pharmacogalenical properties, such as good solubility in various solvents. An active compound of the present invention, in particular a compound of formula I wherein R_4 is other than hydrogen, may have surprising stability in vivo environment as may be determined by the determination of stability in plasma.

In another aspect the present invention provides an active compound of the present invention for use as a pharmaceutical, preferably in indications of IgE mediated diseases.

The active compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt, e.g. an acid addition salt or metal salt; or in free form; optionally in the form of a solvate. The active compounds of the present invention in the form of a salt exhibit the same order of activity as the active compounds of the present invention in free form; optionally in the form of a solvate.

In another aspect the present invention provides a pharmaceutical composition comprising an active compound of the present invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured according to a method as conventional.

In the following examples which illustrate the invention references to temperature are in degrees Celsius. The following abbreviations are used:
m.p. = melting point RT = room temperature

Example 1

N-[4-(3-Chloro-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-amine

A) 1-(3-Chloro-phenyl)-3-dimethylamino-propenone

A mixture of 50 g of 3-chloroacetophenone and 65 ml of N,N-dimethylformamide dimethyl acetal is heated at ca. 100° for ca. 24 hours and cooled to RT. A precipitate formed is filtrated off, washed and dried. 40 g of 1-(3-chloro-phenyl)-3-dimethylamino-propenone in crystalline form are obtained. m.p. 72.8°.

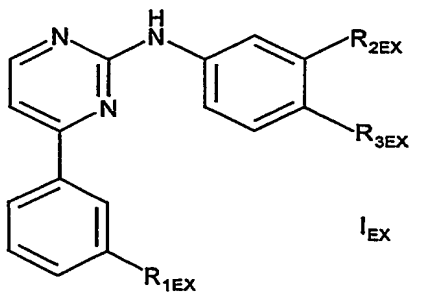
B) N-(4-Trifluoromethyl-phenyl)-guanidine carbonate

13.75 ml of aqueous 37% HCl are added dropwise to a mixture of 17.5 ml of 4-trifluoromethylaniline and 28 ml of water, preheated to ca. 75° for ca. 20 minutes. To the mixture obtained a solution of 12.9 g of cyanamide in 13 ml of water is added dropwise at ca. 75° and stirring is continued for ca. 4 hours at that temperature. The mixture obtained is cooled to RT and a solution of 9.26 g of Na_2CO_3 in 43 ml of water are added dropwise. To the mixture obtained 140 ml of water are added and the mixture obtained is stirred overnight. A solid precipitates, is filtrated off, washed and dried. 14 g of N-(4-trifluoromethyl-phenyl)-guanidine carbonate in crystalline form are obtained. m.p. 125.3°.

C) N-[4-(3-Chloro-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-amine

A mixture of 1.5 g of 1-(3-chloro-phenyl)-3-dimethylamino-propenone, 1.7 g of of N-(4-trifluoromethyl-phenyl)-guanidine carbonate and 15 ml of n-butanol is heated at 120° for ca. 24 hours, the mixture obtained is cooled to RT and a solid precipitates. The precipitate is filtrated off and is re-crystallised from n-butanol. 1.0 g of N-[4-(3-chloro-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-amine in crystalline form are obtained. m.p. 201.5°.

Analogously as described in example 1 but using appropriate starting material, compounds of formula



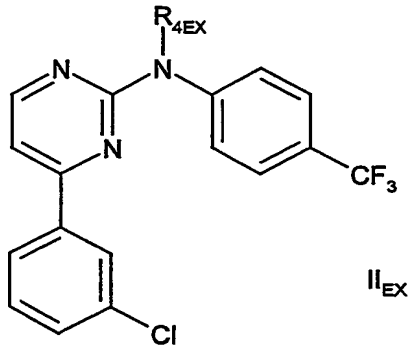
I_{EX}

wherein R_{1EX}, R_{2EX} and R_{3EX} are as defined in TABLE 1 below having a melting point m.p. as defined in TABLE 1 below are obtained:

TABLE 1

Example	R_{1EX}	R_{2EX}	R_{3EX}	m.p. (°)
2	CF_3	CF_3	F	168.0
3	Cl	CF_3	Cl	182.3
4	CF_3	CF_3	Cl	161.8
5	CF_3	H	CF_3	185.9

Starting from a compound of formula



II_{EX}

wherein R_4 is hydrogen, which is the compound [4-(3-chloro-phenyl)-pyrimidin-2-yl]-(4-trifluoromethyl-phenyl)-amine, compounds as described in the following examples 6 to 43, wherein R_4 is other than hydrogen adn defined in said examples, may be obtained.

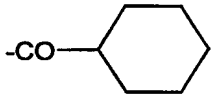
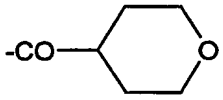
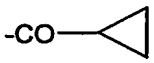
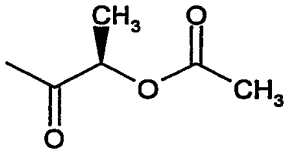
Example 6

Compound of formula II_{EX}, wherein R_{4EX} is a group of formula -CO-CH_3
N-[4-(3-Chloro-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-acetamide

A solution of 1.6 g of a compound of formula II_{EX} wherein R_4 is hydrogen and 300 mg of 4-dimethylaminopyrimidine in 30 ml of dry pyridine is treated with acetic acid anhydrid and stirred at 70°. From the mixture obtained solvent is evaporated off, diethyl ether is added and a precipitate obtained is removed by filtration . The filtrate obtained is concentrated and the concentrate obtained is subjected to silicagel medium pressure chromatography. N-[4-(3-Chloro-phenyl)-pyrimidin-2-yl]-N-(4-trifluoromethyl-phenyl)-acetamide is obtained in solid (crystalline) form from a mixture of toluene and pentane in the form of a powder . m.p. 128.6 - 129.6°.

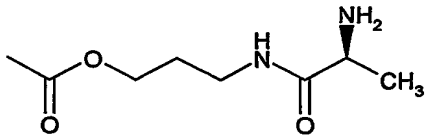
Analogously to the method as described in example 6, but using appropriate starting materials, compounds of formula II_{EX}, wherein R_{4EX} is as described in TABLE 2 below, having ^{1}H-NMR or m.p. data as defined in TABLE 2 are obtained:

TABLE 2

Example	R_{4EX}	m.p. / ^{1}H-NMR
7	-CO-CH_2-CH_3	121.1°
8	-CO-$CH(CH_3)_2$	122-122.8°
9	-CO-C_6H_5	130.1°
10	-CO-CH_2-$CH(CH_3)_2$	109-110°
11	-CO-CO-C_6H_5	144.9°
12	-CO-$C(CH_3)_3$	103.9-104.7°
13		136.8°
14		158.8°
15	-CO-CO-O-CH_2-CH_3	133.7°
16	-CO-CH_2-O-CO-CH_3	150.8°
17	-CO-CO-O-CH_3	141.3°
18		94.5-95.8°
19	-CO-CH_2-O-CH_3	124.6°
20		^{1}H-NMR (d_6-DMSO, 400 MHz, rt) □: 8.96(d, J=5.3,1H), 8.15(d, J=5.3,1H), 7.95(d, J=8.3,2H), 7.70(t,J= 7.8,1H), 7.60 (d, J=8.2,2H), 5.97 (q, J=6.7,1H), 2.06(s,3H), 1.69(d, J=6.7,3H)

Example 21

Compound of formula II_{EX}, wherein R_{4EX} is a group of formula



4-(3-Chloro-phenyl)-pyrimidin-2-yl]-(4-trifluoromethyl-phenyl)-carbamic acid 3-((S)-2-tert.-butoxycarbonylamino-propionylamino)-propyl ester in the form of a free base and in the form of a hydrochloride

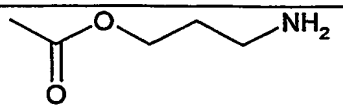
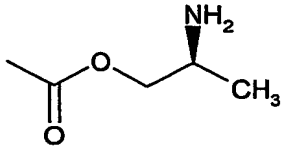
0.5 g of a solution of a compound of formula II_{EX} wherein R_4 is hydrogen in 30 ml of dry chlorbenzene is treated with a solution of 0.76 ml of 20% phosgen in toluene. The mixture

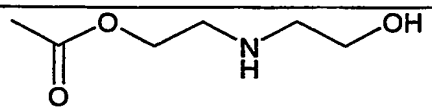
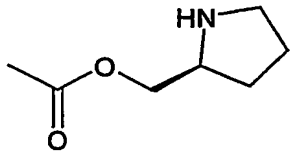
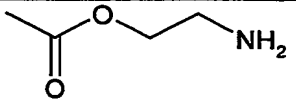
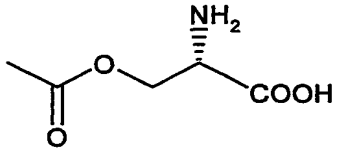
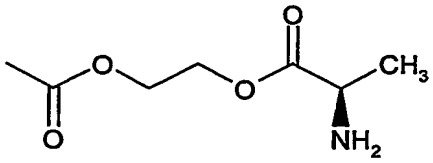
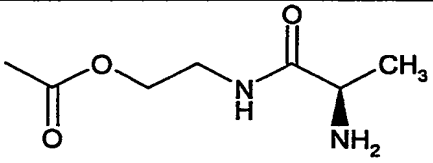
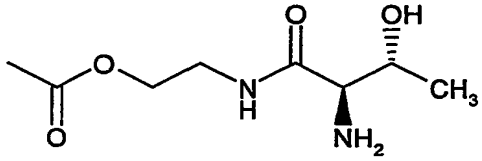
obtained is stirred at 130°, a clear solution obtained is cooled to 100° and a further solution of 0.76 ml of 20% phosgen in toluene is added. The mixture obtained is stirred at 130°, cooled to 100° and purged with argon in order to remove excess phosgen. To the mixture obtained a solution of 144 µl of [(S)-1-(3-hydroxy-propylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester and 130 µl of pyridine in 5 ml of chlorbenzene is added, the mixture obtained is stirred at 130° and cooled to RT. The mixture obtained is washed with 1N aqueous HCl, aqueous, saturated $NaHCO_3$ solution and brine and concentrated. The concentrate obtained is subjected to flash chromatography on silicagel. [4-(3-Chloro-phenyl)-pyrimidin-2-yl]-(4-trifluoromethyl-phenyl)-carbamic acid 3-((S)-2-tert.-butoxycarbonylamino-propionylamino)-propyl ester is obtained in the form of an oil.
^{1}H-NMR ($CDCl_3$, 400 MHz, rt) δ: 8.77(d;1H), 7.94(s;1H), 7.83(d;1H), 7.69(d;1H), 7.51(d; 1H), 7.50-7.38(m;4H), 4.35(t;2H), 3.16(m;2H), 1.84(m;2H), 1.43(s;9H).

276 mg of a solution of [4-(3-chloro-phenyl)-pyrimidin-2-yl]-(4-trifluoromethyl-phenyl)-carbamic acid 3-((S)-2-tert.-butoxycarbonylamino-propionylamino)-propyl ester in trifluoroacetic acid is stirred for ca. 2 hours. From the mixture obtained solvent is evaporated off and the evaporation residue obtained is dissolved in diethyl ether. The mixture obtained is treated with HCl in diethyl ether. [4-(3-Chloro-phenyl)-pyrimidin-2-yl]-(4-trifluoromethyl-phenyl)-carbamic acid 3-((S)-2-tert.-butoxycarbonylamino-propionylamino)-propyl ester in the form of a hydrochloride precipitates, is filtrated off, washed and dried. m.p.: 54.6-54.8°.

Analogously to the method as described in example 21, but using appropriate starting materials, compounds of formula II_{EX}, wherein R_{4EX} is as described in TABLE 3 below, having ^{1}H-NMR or m.p. data as defined in TABLE 3 are obtained:

TABLE 3

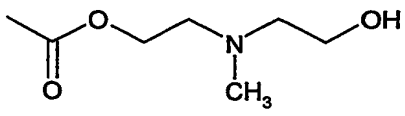
Example	R_{4EX}	m.p. / ^{1}H-NMR
22		65.7-72.9°
23		192.5-194.2°

Example	R_{4EX}	m.p. / ^{1}H-NMR
24		191.9-193.7°
25		126.8-130.8°
26		161-162.8°
27		138.1-143.2°
28		^{1}H-NMR (DMSO-d6, 400 MHz, rt) δ: 8.86(d;1H), 8.44(bd;3H), 8.15(m;1H), 8.10(m;1H), 8.06(d;1H), 7.76/7.51 (AB-system;4H), 7.64(m;1H), 7.57(t;1H), 4.62-4.36(m;3H), 4.32-4.28(m;1H), 4.02-3.98(m;1H), 1.26(d;3H)
29		133-136.3°
30		91.9-95°

In TABLE 3 the m.p. or ^{1}H-NMR data is the data of the compounds of examples 22 to 30 in the form of hydrochlorides.

Example 31

Compound of formula II_{EX}, wherein R_{4EX} is a group of formula

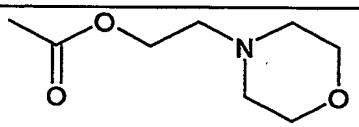
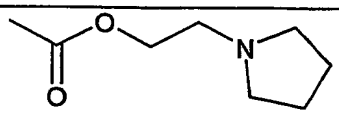
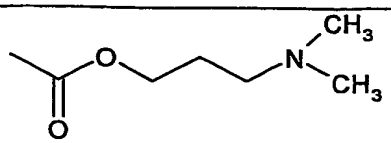


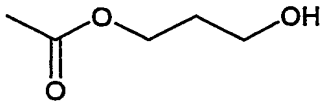
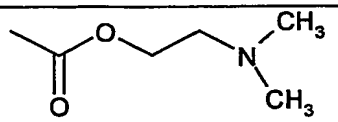
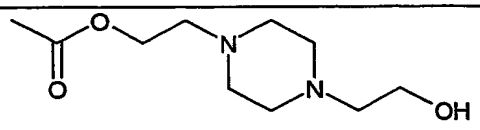
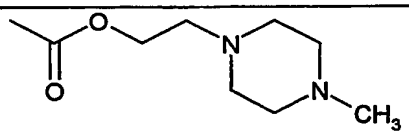
[4-(3-Chloro-phenyl)-pyrimidin-2-yl]-(4-trifluoromethyl-phenyl)-carbamic acid 2-[(2-hydroxy-ethyl)-methyl-amino]-ethyl ester in the form of a hydrochloride

0.5 g of a solution of a compound of formula II_{EX} wherein R_4 is hydrogen in 30 ml of dry chlorbenzene is treated with a solution of 0.76 ml of 20% phosgen in toluene. The mixture obtained is stirred at 130°, a clear solution obtained is cooled to 100° and a further solution of 0.76 ml of 20% phosgen in toluene is added. The mixture obtained is stirred at 130°, cooled to 100° and purged with argon in order to remove excess phosgen. The mixture obtained is treated at RT with 0.675 ml of a solution of 2-[(2-hydroxy-ethyl)-methyl-amino]-ethanol in 5 ml of chlorbenzene and stirred at 130°, cooled to RT and concentrated in vacuum. The concentration residue obtained is dissolved in ethyl acetate and washed with aqueous, saturated $NaHCO_3$ solution and brine. The organic layer obtained is treated with acetic acid, the mixture obtained is concentrated in vaccum and the concentrate obtained is subjected to chromatography. [4-(3-Chloro-phenyl)-pyrimidin-2-yl]-(4-trifluoromethyl-phenyl)-carbamic acid 2-[(2-hydroxy-ethyl)-methyl-amino]-ethyl ester in the form of an acetate obtained is dissolved in diethy ether and treated with HCl in diethyl ether. [4-(3-Chloro-phenyl)-pyrimidin-2-yl]-(4-trifluoromethyl-phenyl)-carbamic acid 2-[(2-hydroxy-ethyl)-methyl-amino]-ethyl ester in the form of a hydrochloride precipitates (crystallizes), is filtrated off, washed and dried. m.p.: 145.9 - 147.7°.

Analogously to the method as described in example 31, but using appropriate starting materials, compounds of formula II_{EX}, wherein R_{4EX} is as described in TABLE 4 below, having ^{1}H-NMR or m.p. data as defined in TABLE 4 are obtained:

TABLE 4

Example	R_{4EX}	m.p. / ^{1}H-NMR
32	-CO-O-CH_2-CH_3	68.3-69.2°
33		151.3-154.3°
34		171.2-174.3°
35		128.9-129.1°

Example	R_{4EX}	m.p. / ^{1}H-NMR
36		^{1}H-NMR (DMSO-d6, 400 MHz, rt) δ: 8.85(d;1H), 8.15(m;1H), 8.10(m;1H), 8.04(d;1H), 7.75/7.48 (AB-system,4H); 7.63(m;1H), 7.57(t;1H), 4.46(t;1H), 4.25(t;2H), 3.34(dt;2H), 1.69(d;2H)
37		152.7-156.2°
38		154.9-162.8°
39		^{1}H-NMR (DMSO-d6, 400 MHz, rt) δ: 8.86(d;1H), 8.11-8.05(m;3H), 7.79(d; 2H); 7.64 –7.57(m;4H), 4.62(bs;2H), 3.60-3.40(m;8H), 3.40-3.25(m;2H), 2.76 (s; 3H)

In TABLE 4 the m.p. or ^{1}H-NMR data of examples 32, 36 and 39 is the data of the compounds in free base form, the m.p. or ^{1}H-NMR data of examples 33, 34, 35, 37 and 38 is the data of the compounds in the form of hydrochlorides.

Example 40

Compound of formula II_{EX}, wherein R_{4EX} is -CH_3

[4-(3-Chloro-phenyl)-pyrimidin-2-yl]-methyl-(4-trifluoromethyl-phenyl)-amine

A solution of 160 mg of a compound of formula II_{EX} wherein R_4 is hydrogen in 4 ml of dry dimethylformamide is treated with NaH, the mixture obtained is stirred at 100°, cooled to RT and treated with 57µl of methyliodide. The mixture obtained is stirred overnight at RT. From the mixture obtained a precipitate is filtrated off and the filtrate obtained is concentrated in vaccum. The concentration residue obtained is subjected to flash chromatography on silicagel. [4-(3-Chloro-phenyl)-pyrimidin-2-yl]-methyl-(4-trifluoromethyl-phenyl)-amine obtained is precipitated from n-pentane in the form of a solid, filtrated off and dried. Structure confirmed by ^{1}H-NMR data.

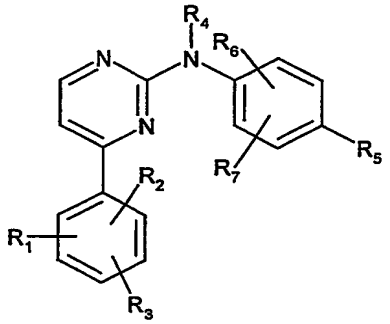
Analogously to the method as described in example 40, but using appropriate starting materials, compounds of formula II_{EX}, wherein R_{4EX} is as described in TABLE 5 below, having ^{1}H-NMR or m.p. data as defined in TABLE 5 are obtained:

TABLE 5

Example	R_{4EX}	m.p. / ^{1}H-NMR
41	$-CH_2-CH_2-OH$	86.2°
42	$-S(O)_2-CH_3$	152.7-153.2°
43	$-CO-N(CH_3)_2$	143°

Patent Claims

1. A compound of formula



I

wherein

at least one of R_1, R_2 and R_3 is halogen or haloalkyl, and the other of R_1, R_2 and/or R_3 are independently of each other hydrogen, halogen or haloalkyl,

R_5 is halogen or haloalkyl,

R_6 and R_7 independently of each other are hydrogen, halogen, or haloalkyl, and

R_4 is hydrogen, alkyl, or a group of formula -CO-R_8, -CO-OR_9, -CO-CO-R_{10}, -CO-CO-OR_{11}, -CO-O-CO-R_{12}, -CO-N($R_{13}R_{14}$) or -SO_2-R_{15}, wherein

R_8, R_9 independently of each other are hydrogen, alkyl, cycloalkyl, aryl or heterocyclyl,

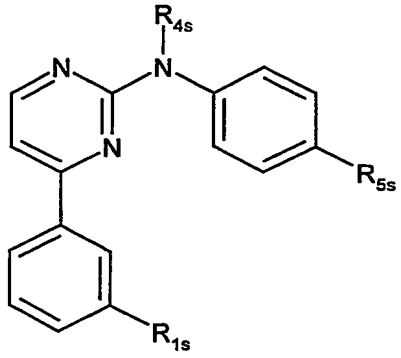
R_{10}, R_{11} and R_{12} independently of each other are alky, cycloalkyl, aryl or heterocyclyl,

R_{13} and R_{14} independently of each other are hydrogen ore alkyl, or

one of R_{13} and R_{14} is hydrogen and the other is cycloalkyl, aryl or heterocyclyl, and

R_{15} is hydroxy, alkyl or aryl.

2. A compound of claim 1 which is a compound of formula



Is

wherein

R_{1s} is halogen or haloalkyl, preferably halogen, R_{5s} is halogen or haloalkyl, preferably haloalkyl and R_{4s} has the meaning of R_4 as defined in claim 1.

3. A compound of claim 2 wherein R_{1s} is chloro, R_{5s} is trifluoromethyl and R_{4s} has the meaning of R_4 as defined in claim 1.

4. A compound of any one of claims 1 to 3 in the form of a salt, or in the form of a salt and in the form of a solvate, or in the form of a solvate.

5. Use of a compound of any one of claims 1 to 5 in the preparation of a medicament for the therapy of IgE-mediated diseases, e.g. of diseases mediated by IgE expression.

6. A method of treatment of IgE-mediated diseases which comprises administering a therapeutically effective amount of a compound of any one of claims 1 to 3 to a subject in need of such treatment.

7. A compound of any one of claims 1 to 4 for use as a pharmaceutical.

8. A pharmaceutical composition comprising a compound of any one of claims 1 to 4 in association with at least one pharmaceutical carrier or diluent.

9. Use of an amine, which is substituted by
- phenyl-substituted pyrimidin; and
- phenyl; and
- hydrogen or a third substituent,
in the preparation of a medicament for the treatment of IgE-synthesis-mediated diseases.

Abstract

Use of an amine, which is substituted by phenyl-substituted pyrimidin; and phenyl; and hydrogen or a third substituent, in the preparation of a medicament for the treatment of IgE-synthesis-mediated diseases.

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